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Decreased GABA-A receptor binding in association with β -lactam antibiotic use

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Compliance with Ethical Standards

- The authors declare that they have no conflict of interest.
- Informed consent was obtained from all individual participants included in the study.
- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Decreased GABA-A receptor binding in association with β -lactam antibiotic use

Abstract : β -lactam antibiotics are proconvulsive. In laboratory animals, this effect appears to be predominantly mediated through inhibition of GABA-A receptors, but it has not been demonstrated in humans in vivo. We report images of a [^{11}C]Ro15-4513 PET from a 40 years old male who had completed a one week course of flucloxacillin before it. Relative to healthy controls, the participant had significantly lower mean grey matter binding. These novel data suggest that in humans, the proconvulsive effect of β -lactam antibiotics is mediated via either competition for the same benzodiazepine binding site as [^{11}C]Ro15-4513, or downregulation of GABA-A receptor expression.

Keywords : PET; Ro15-4513; β -lactam; GABA-A

FIGURE 1. β -lactam antibiotics such as flucloxacillin are proconvulsive, and seizures are a well-recognized manifestation of penicillin neurotoxicity[1,2]. In laboratory animals, this effect appears to be predominantly mediated through inhibition of GABA-A receptors[3–5]. However, to our knowledge, the effect of β -lactam antibiotics on GABA-A receptor binding has not been demonstrated in humans *in vivo*.

[^{11}C]Ro15-4513 was used to acquire positron emission (PET) data from a 40-year-old male who had completed a one-week course of flucloxacillin 250mg q.i.d. one day before the scan. Data were acquired as described previously[6]. [^{11}C]Ro15-4513 volume-of-distribution (V_T ; i.e. binding) reflects the availability of GABA-A receptor subunit: total, $\alpha 1$ (mostly fast), and $\alpha 5$ (mostly slow) components [7]. We corrected for partial volume effects using SFS-RR[8].

Relative to 23 unmedicated healthy controls, the participant had significantly lower mean grey matter total V_T (-30% [3.39 vs. mean \pm standard deviation 4.86 ± 0.51], $p=0.002$). The reduction was of similar magnitude for both fast and slow mean grey matter V_T s (fast: -29% [2.10 vs. 2.94 ± 0.29], $p=0.002$; slow: -31% [1.24 vs. 1.81 ± 0.60], $p=0.174$).

The participant's injectate had contained 17.05 μg of ligand, whereas $3.44 \pm 1.34 \mu\text{g}$ was typical for the healthy controls. This cannot explain our findings, as $\alpha 5$ subunit occupancy was $\sim 11.9\%$, and $\alpha 1$ occupancy only $\sim 1.0\%$, with a near-identical reduction for both components.

These novel data suggest that in humans, the proconvulsive effect of β -lactam antibiotics is mediated via either competition for the same benzodiazepine binding site as [^{11}C]Ro15-4513, or downregulation of GABA-A receptor expression.

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